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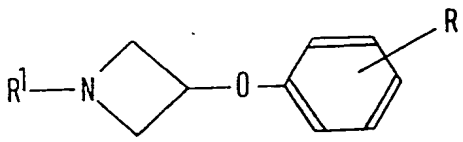
(54) **1-R¹-3-phenoxyazetidines**

(57) 1-R¹-3-phenoxyazetidines having the formula:



wherein R represents a hydrogen atom or a chloro atom or an aminocarbonyl, cyano or trifluoromethyl group and R¹ represents an α-methylbenzyl or diphenylmethyl group and salts thereof, are useful in the preparation of corresponding compounds in which R¹ is H which are anorexigenic agents.

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The chemical formulae appearing in the printed specification were submitted after the date of filing, the formulae originally submitted being incapable of being satisfactorily reproduced.

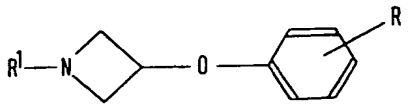
SPECIFICATION

1-R¹-3-Phenoxyazetidines

The present invention relates to certain novel heterocyclic compounds and more particularly to 1-R¹-3-phenoxyazetidines, compositions thereof, and methods of making and using same.

German Offenlengungsschrift 2,317,980 discloses N-oxides of N-substituted azetidine compounds and their use as intermediates for the preparation of 2-substituted isoxazolidines.

The invention provides 1-R¹-3-phenoxyazetidines having the formula:

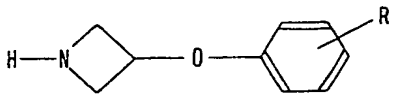


wherein:

R¹ represents an α-methyl benzyl or diphenylmethyl group; and

R represents a hydrogen or a chloro atom or an aminocarbonyl, cyano or trifluoromethyl group.

The compounds of the present invention of Formula I are useful as intermediates for the preparation of novel 3-phenoxyazetidine compounds having the formula:



Formula II

wherein:

R represents a hydrogen atom or an aminocarbonyl or trifluoromethyl group, and pharmaceutically acceptable acid addition salts thereof.

The compounds of Formula II are useful because of their pharmacological action on the central nervous system. In particular, the compounds have anorexigenic activity.

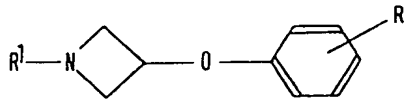
The compounds of Formula II are described and claimed in our copending application No. 8032436.

The anorexigenic property was determined according to the procedure of Roszkowski and Kelly, A Rapid Method for Assessing Drug Inhibition, J. Pharmacol. Exptl. Therap. *140*, 367—374 (1963) as modified by Alphin and Ward, Anorexigenic Effects of Fenfluramine Hydrochloride in Rats, Guinea Pigs and Dogs, Toxicology and Applied Pharmacology *14*, 182—191 (1969). Among the compounds of Formula II which have shown good activity in the aforementioned test is the representative compound 3-phenoxyazetidine.

It is, therefore, an object of the present invention to provide certain novel 1-R¹-3-phenoxyazetidines, useful in the production of novel 3-phenoxyazetidines having anorexigenic activity.

This invention also includes pharmaceutically acceptable acid addition salts of the compounds of Formula I. Such acid addition salts are easily prepared by methods known in the art and can be derived from various organic and inorganic acids such as citric, acetic, lactic, maleic, fumaric, benzoic, tartaric, ascorbic, pamoic, succinic, methanesulphonic, malic, citraconic, itaconic acid, hydrochloric, hydrobromic, sulphuric, phosphoric, nitric and related acids.

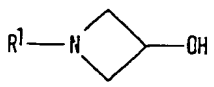
Compounds of Formula II may be conveniently prepared by contacting the appropriate 1-R¹-3-phenoxyazetidines azetidine of the present invention of the formula:



(I)

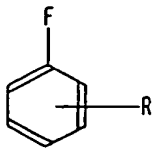
wherein R is defined as hereinbefore and R¹ represents an α-methylbenzyl or diphenylmethyl group with hydrogen in the presence of a palladium on charcoal catalyst. The hydrogenolysis may be carried out in the presence of a lower alkanol solvent, ethanol being preferred. The rate of hydrogenolysis is dependent somewhat on time and temperature, a higher temperature generally decreasing the time required for complete hydrogenolysis. Typical times vary from about 3 hours to about 24 hours with typical temperature varying from about 70°C to about 90°C.

The starting material of Formula (I) may conveniently be prepared by contacting a 1-R¹-3-azetidinol of the formula:



III

wherein R^1 is defined as hereinbefore with the appropriate fluorobenzene of the formula:



IV

wherein R represents a hydrogen or chloro atom or a trifluoromethyl group. The reaction is run at a temperature of from about 80°C to about 100°C and for a period of from about two hours to about five hours. The preferred solvent is dimethylformamide. The starting material of Formula (I) wherein R represents an aminocarbonyl group is preferably prepared by basic hydrolysis of a precursor cyano compound.

The compounds of Formula I and Formula II are basic compounds and are useful for neutralizing acidic solutions.

The following preparations and examples describe in detail compounds illustrative of the present invention and methods which have been devised for their preparation.

EXAMPLE 1

1-(α-methylbenzyl)-3-(3-Chlorophenoxy)-azetidine Oxalate.

1-(α-Methylbenzyl)-3-hydroxyazetidine maleate (393 g, 1.3 moles) was partitioned in dilute potassium hydroxide-benzene. The separated dried benzene solution was concentrated, the residual oil dissolved in 250 ml of dimethylformamide and added dropwise to a stirred suspension of 53 g (1.1 moles) of 50% sodium hydride in 750 ml of dimethylformamide at 90°C. The mixture was heated at 90°C for 1 hour and 130.5 g (1 mole) of 3-chlorofluorobenzene added dropwise at 90°C. The mixture was refluxed for 3 hours, cooled and partitioned between isopropyl ether and dilute sodium hydroxide. The isopropyl ether solution was dried, concentrated, and the residue added to 1200 ml of isopropyl alcohol containing 90 g (1 mole) of oxalic acid. The oxalate salt was recrystallized from ethanol. Yield 263 g (69%); m.p. 141—144°C.

Analysis:

Calculated for $C_{19}H_{20}ClNO_5$:	C, 60.40;	H, 5.34;	N, 3.71
Found:	C, 60.19;	H, 5.55;	N, 3.60

EXAMPLE 2

1-(α-Methylbenzyl)-3-(4-trifluoromethylphenoxy) azetidine.

The maleate salt of 1-(α-methylbenzyl)-3-hydroxyazetidine (78.6 g, 0.20 mole) was partitioned between benzene and dilute sodium hydroxide, the benzene layer dried, filtered, and concentrated at reduced pressure. The residue was dissolved in 100 ml of dry dimethylformamide and added at a rapid dropwise rate, to a stirred suspension of 10.1 g (0.22 mole) of sodium hydride (50% in mineral oil) in 150 ml of dry dimethylformamide at 90°C. The solution was heated at 90°C for one hour and then treated dropwise with 32.0 g (0.20 mole) of 4-trifluoromethylfluorobenzene. The solution was refluxed for three hours. The cooled solution was partitioned between water and isopropyl ether, and the ether layer extracted with dilute hydrochloric acid. The aqueous acid layer was made basic with concentrated sodium hydroxide and ice, and extracted with isopropyl ether. The ether layer was concentrated and the residue distilled at 150—160°C/0.2 mm to give 25.6 g of product.

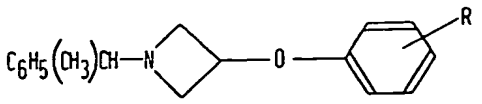
Analysis:

Calculated for $C_{18}H_{18}F_3NO$:	C, 67.28;	H, 5.65;	N, 4.36
Found:	C, 67.27;	H, 5.84;	N, 4.34

EXAMPLES 3 TO 7

These were carried out according to the procedures set forth in detail in Preparations 1 and 2 by reacting 1-(α-methylbenzyl)-3-azetidinol with the appropriately substituted fluorobenzene. The physical constants and the R substitutent are shown in Table I.

TABLE I



Example	R	M.P. (b.p.) °C	Salt
3	2-$CONH_2$	148–52	–
4	4-CN	65–8	–
5	3-CF_3	150–3	$(COOH)_2$
6	2-CF_3	162–3	$(COOH)_2$
7	3-CN	[1](185–90)	–

[1] At 0.2 mm Hg. pressure.

The analytical data of Examples 3 to 7 are shown in Table II.

TABLE II

Analytical Data on Examples 3 to 7

Preparation	Empirical Formula	Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
3	$C_{16}H_{20}N_2O_2$	72.95	6.80	9.45	72.56	6.78	9.32
4	$C_{16}H_{16}N_2O$	77.67	6.52	10.06	77.61	6.53	10.01
5	$C_{20}H_{20}F_3NO_5$	58.39	4.90	3.41	57.99	4.97	3.39
6	$C_{20}H_{20}F_3NO_5$	58.39	4.90	3.41	58.15	4.89	3.37
7	$C_{16}H_{16}N_2O$	77.67	6.52	10.06	77 32	6.54	9.87

PREPARATION 1

Use of compound of the invention as an intermediate in the preparation of 4-(Phenoxy)-azetidine Methanesulphonate.

A 200 ml solution of 7.8 g (0.025 mole) of 1-diphenylmethyl-3-phenoxyazetidine in ethanol was treated with 20% Pd $(OH)_2$ on carbon and hydrogenated for 23 hours at about 45 p.s.i. and 80°C. The mixture was filtered and the filtrate concentrated. The residue was diluted to 30 ml with ethanol and 2.5 g of methanesulphonic acid added. The isolated methanesulphonate salt was recrystallized from ethanol. The salt weighed 2.3 g (37.5%) and melted at 128—130°C.

Analysis:

Calculated for $C_{10}H_{15}NO_4S$: C, 48.97; H, 6.16; N, 5.71

Found: C, 48.40; H, 6.19; N, 5.63

The compound was also prepared by hydrogenolysis of 1-(α-methylbenzyl)-3-(3-chlorophenoxy) azetidine in isopropyl alcohol using the same type catalyst and conditions.

PREPARATION 2

3-[4-(Trifluoromethyl)phenoxy]azetidine Oxalate.

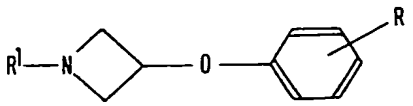
To 24.0 g (0.075 mole) of 1-(α-methylbenzyl)-3-4-(trifluoromethyl)phenoxy -azetidine in 150 ml of ethanol was added 0.5 g of 20% Pd $(OH)_2$ on carbon, and the mixture was hydrogenated for five hours at 80°C and 45 p.s.i. The mixture was cooled, filtered, and the filtrate concentrated at reduced pressure. The residue was dissolved in ethanol and treated with oxalic acid, and the oxalate salt was recrystallized three times in ethanol. The yield was 3.0 g (13%) and the salt melted at 176—178°C.

Analysis:

Calculated for $C_{12}H_{12}F_3NO_3$:	C, 46.91;	H, 3.94;	N, 4.56
Found:	C, 47.07;	H, 3.96;	N, 4.59

CLAIMS

1. 1-R^1-3-phenoxyazetidines having the formula:



wherein:

R^1 represents an α-methylbenzyl or diphenylmethyl group; and

R represents a hydrogen or a chloro atom or an aminocarbonyl, cyano or trifluoromethyl group, or a salt thereof.

2. 1-(α-Methylbenzyl)-3-(3-chlorophenoxy)-azetidine.
3. 1-(α-Methylbenzyl)-3-(3-chlorophenoxy)-azetidine oxalate.
4. 1-(α-Methylbenzyl)-3-(4-trifluoromethylphenoxy)-azetidine.
5. 1-(α-Methylbenzyl)-3-(2-aminocarbonylphenoxy)-azetidine.
6. 1-(α-Methylbenzyl)-3-[4-(cyano)phenoxy]-azetidine.
7. 1-(α-Methylbenzyl)-3-[3-(trifluoromethyl)-phenoxy]azetidine.
8. 1-(α-Methylbenzyl)-3-[2-(trifluoromethyl)-phenoxy]azetidine.
9. 1-(α-Methylbenzyl)-3-[3-(cyano)phenoxy]-azetidine.
10. 1-Diphenylmethyl-3-phenoxyazetidine.
11. 1-(α-Methylbenzyl)-3-[4-(trifluoromethyl)-phenoxy]azetidine.
12. A compound as claimed in Claim 1 whenever prepared by a method as described in any one of Examples 1 to 7.

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